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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUL 15 1987

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: Review of the pharmacokinetic study in mice on 2,4-D

To: Lynn Vlier
Special Review
Registration Division, TS-767C

From: Marcia van Gemert, Ph.D. M. van Gemert 7/7/87
Head, Section III
Toxicology Branch, HED

Thru: Theodore M. Farber, Ph.D. W. Burnam 7/15/87
Chief, Toxicology Branch, HED

Chemical: 2,4-Dichlorophenoxyacetic acid

The Industry Task Force on 2,4-D Research Data submitted a pharmacokinetic study on 2,4-D in mice. The DER for this study is attached. In mice, urine appears to be the major excretory route, with elimination at low doses following the Michaelis-Menten two compartment model. At higher doses, the urinary excretory mechanism appears to be saturable, and the Michaelis-Menten clearance doesn't fit.

Reviewed by: Marcia van Gemert, Ph.D. M. van Gemert 7/6/87
Head, Section III, Tox. Branch (TS-769C)
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DATA EVALUATION REPORT

STUDY TYPE: Pharmacokinetic study in mice TOX CHEM NO: 315

ACCESSION NUMBER: 256267 MRID NO: ?

TEST MATERIAL: 2,4-Dichlorophenoxyacetic acid

SYNONYMS: 2,4-D

STUDY NUMBER: 2184-104

SPONSOR: Industry Task Force on 2,4-D Research Data

TESTING FACILITY: Hazleton Laboratories, Vienna, Va.

TITLE OF REPORT: The pharmacokinetic evaluation of ^{14}C-2,4-Dichlorophenoxyacetic acid (2,4-D) in the mouse

AUTHORS: J. L. Eiseman

REPORT ISSUED: 8/15/84

CONCLUSIONS: 2,4-D was given to $B_6C_3F_1$ mice at doses of 5, 45 and 90 mg/kg. The pharmacokinetics of elimination at low doses resembled the Michaelis-Menten two compartment model. Urine was the major excretory route. At higher doses, the Michaelis-Menten clearance didn't fit, suggesting a saturation of urinary excretion at higher doses.

CLASSIFICATION: minimum

A quality assurance statement was signed and dated 8/15/84

A. MATERIALS:

1. Test Compound: Labeled, acid ring-UL-^{14}C, monosodium salt
   Description: beige granular, Specific activity = 9.7 mCi/mMole or 39.92 uCi/mg
   Batch #:8.30718
   Purity: 96%
   Source: Pathfinders Laboratories, St. Louis, Mo.
   Unlabeled: Batch # 19737B, Beige very fine powder.

2. Test Animals:
   Species: mouse
   Strain: $B_6C_3F_1$
   Age: 9-10 weeks old at study initiation
   Weight: not given
   Source: Charles River Breeding Laboratories, Canada

3. Dosing preparation and administration data are on appended pages 1-8.

4. Study design: 5 males/group were used and given 5, 45 or 90 mg/kg 2,4-D salt stock solution for the excretion balance study. For the pharmacokinetic study, the doses of 5, 45 or 90 mg/kg were used. For the intravenous pharmacokinetic study, 5, or 90 mg/kg were used.

Procedures for collection and preparation of urine and fecal samples and tissue/organ samples and analysis of radioactivity and pharmacokinetic analysis are on appended pages 9-15.

Results: Results of the mean excretion balance study are on appended pages 16 and 17. Urine samples were taken pre-dose, 0-6, 6-12, 12-24, 24-36, 36-48, 48-72 hours and every 24 hours thereafter up to 168 hours (7 days). Fecal samples were taken predosing, 0-12, 12-24, 24-48, 48-72 hours and every 24 hours thereafter until 168 hours (7 days). Results indicated that the major route of elimination of the ^{14}C-2,4-D was urine, which accounted for 63.08, 83.86, 70.82, 53.07 and 65.31% of the dose excreted from 5, mg/kg oral, 5 mg/kg IV, 45 mg/kg oral, 90 mg/kg oral and 90 mg/kg IV respectively. Fecal elimination accounted for 7.57% (range of 4.29 to 12.64%) of oral 5 mg/kg dose and 5.19% (range 2.72 to 7.32%) of the 5 mg/kg IV dose. At higher doses, a larger proportion of radioactivity appeared in the feces, or 14.9% for 45 mg/kg oral, 16.37% for 90 mg/kg oral and 11.87% for 90 mg/kg IV.

As can be seen on appended pages 18 and 19, the largest proportion of radioactivity in the 5 mg/kg group was excreted in urine in the 0-6 hour time period, whereas at the 90 mg/kg dose, both oral and IV, the majority of radioactivity was eliminated between 6 and 24 hours. The middle doses fell somewhere in between 5 and 90 mg/kg in regard to urinary excretion time.

Concerning deposition of radioactivity in tissues, at doses of 5, 45 and 90 mg/kg almost undetectable amounts of radioactivity were found at any dose at 168 hours post-dosing. However, when mice

were sacrificed at various times post dosing, kidney appeared to contain as much or more radioactivity at 5 mg/kg dose than plasma while liver levels were lower than plasma for the first 6 hours. After 6 hours both liver and kidney contained higher amounts of radioactivity per gram tissue than did plasma. Results are on appended pages 20-27. After a 45 mg/kg dose, liver and kidney contained lower amounts of radioactivity than plasma for the first 4 hours. At 6 hours and later, kidney contained higher levels of radioactivity and beyond 12 hours liver also contained higher levels of radioactivity than plasma. At 90 mg/kg oral plasma radioactivity was higher than liver and kidney for the first 8 hours. After 8 hours both liver and kidney radioactivity were higher than plasma. 90 mg/kg IV plasma levels were higher than kidney for the first 8 hours and liver for the first 12 hours. Thereafter, liver and kidney levels were higher than plasma levels in liver and kidney levels were higher than plasma levels. Levels in liver and kidney after 24 hours were approximately the same magnitude and increased with increasing dose. The study text stated that these data support the theory of a saturability of the excretion mechanism of 2,4-D and chose a 2-compartment model with Michaelis-Menten limited clearance as approximating renal clearance of 2,4-D at low doses, but this was probably too simplistic for clearance at higher doses.

The apparent volumes of distribution were calculated and increased with increasing dose level. For 5 mg/kg the V_D was 142.82 ml/kg for 45 mg/kg the V_D was 213.02 ml/kg; for 90 mg/kg the V_D oral was 299.9 ml/kg; the 90 mg/kg IV V_D was 262.98 ml/kg.

The half-life of absorption ($T_{Ka/2}$) of 2,4-D from the gut was 0.013 hours.

Discussion:
The urinary clearance appears to be saturable, with a smaller percentage of the administered dose being excreted in urine with increasing dose, and greater quantities appearing in the feces. Based on pharmacokinetic calculations, the process of clearance of 2,4-D probably does not follow the simple Michaelis-Menten two compartment model for limited clearance.

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